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ORGANIC CHEMISTRY

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Organic Chemistry

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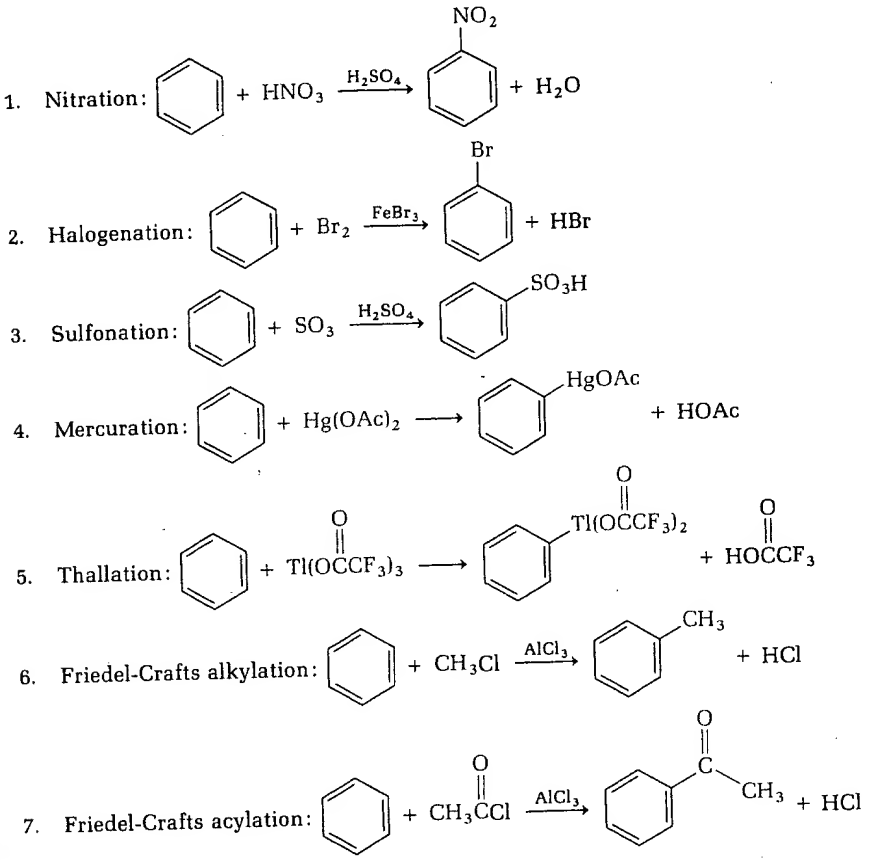
Chart 20·1 Electrophilic Substitution Reactions



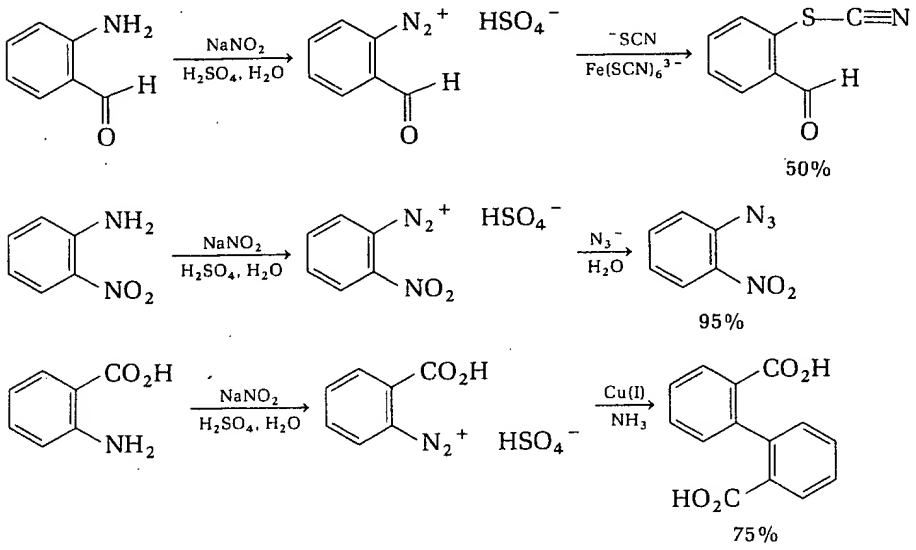
Among the more important types of electrophilic substitution are Friedel-Crafts alkylation and acylation, reactions that generate C—C bonds to the benzene nucleus. They are discussed in detail in Chapter 22.

One of the unusual features of these reactions is the requirement of highly acidic solvents, such as sulfuric acid, or of a special catalyst, such as aluminum chloride, which is a powerful Lewis acid. As we shall see, these conditions are necessary to generate the strong electrophiles needed to attack the stabilized benzene function.

20·12 Activation and Orientation Rules

If an electrophilic aromatic substitution reaction is run on a monosubstituted benzene derivative instead of on benzene itself, we must ask two questions: How fast is the reaction likely to be relative to the reaction with benzene? Which of the three products, ortho, meta, or para, is likely to be formed? No matter what electrophile Y^+ is studied, three rules are sufficient to answer both questions.

RULE 1 ACTIVATING SUBSTITUENTS A benzene derivative substituted with an electron-donating substituent reacts more rapidly than benzene and gives a



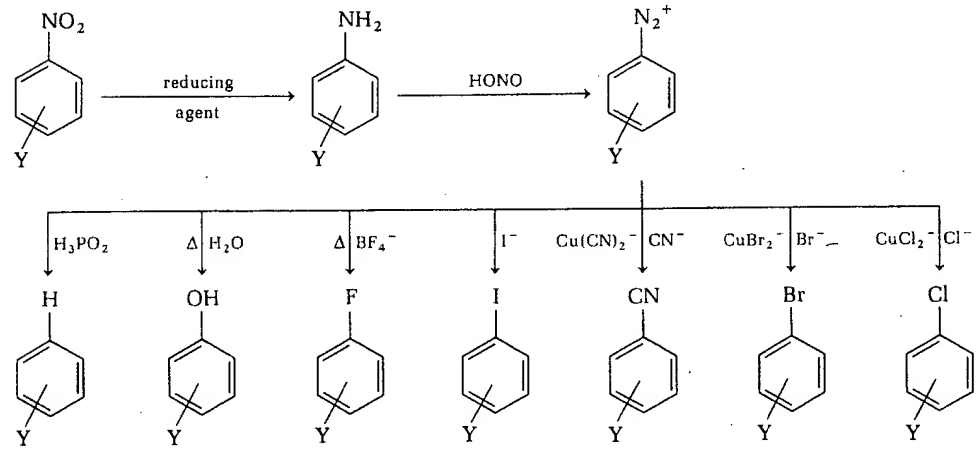


Figure 21·1
Summary of transformations via diazonium salts.

Synthetic Routes to Benzene Derivatives

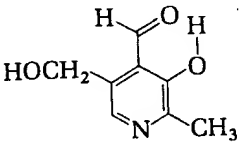
21·8 Synthesis with the $NO_2 \rightarrow NH_2$ Conversion

The reduction of nitrobenzene derivatives to anilines is a key step in the diazonium-salt–mediated replacement of nitro by other functional groups. This reaction converts a meta-directing nitro group into an ortho-para–directing amino group. For this reason, its inclusion in a synthesis gives us one means of controlling orientation. Let us see how.

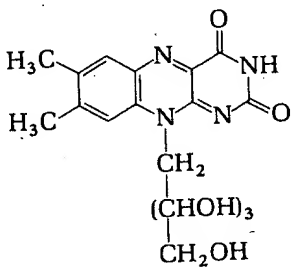
Electrophilic aromatic substitution on nitrobenzene gives us meta isomers, as seen in Figure 21·2. Reduction of the nitro groups to amino groups

gens or other heteroatoms bonded together. The tetrazoles, with four bonded nitrogens, are the most striking examples.

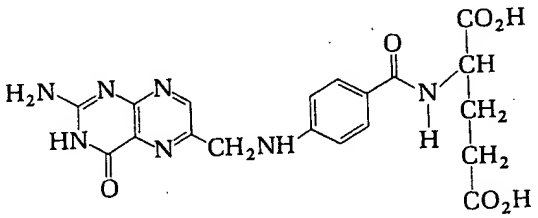
Many derivatives of pyridine, pyrimidine, pyrrole, imidazole, thiazole, and oxazole are important biochemical intermediates. We have seen that vitamin B_1 (thiamin) contains both thiazole and pyrimidine functions (Chapter 26). We saw some imidazole, pyrazine, and pyrimidine derivatives in Chapter 28. Other examples are



Pyridoxal, vitamin B_6



Riboflavin, vitamin B_2



Folic acid
(essential dietary factor)

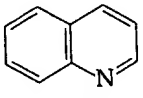
Problem 34·16 Give structures for:

(a) 1,2,4-Triazene (b) 1,3,4-Thiadiazole (c) Pentazole (unstable)

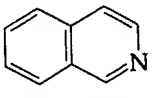
34·11 Pyridine

The chemistry of pyridine and its homologs is the most extensively explored field in heterocyclic chemistry. By examining a few of its highlights, we can find strong analogies with benzene chemistry, with one added feature, the tertiary amine function:

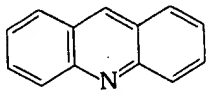
Pyridine



Quinoline

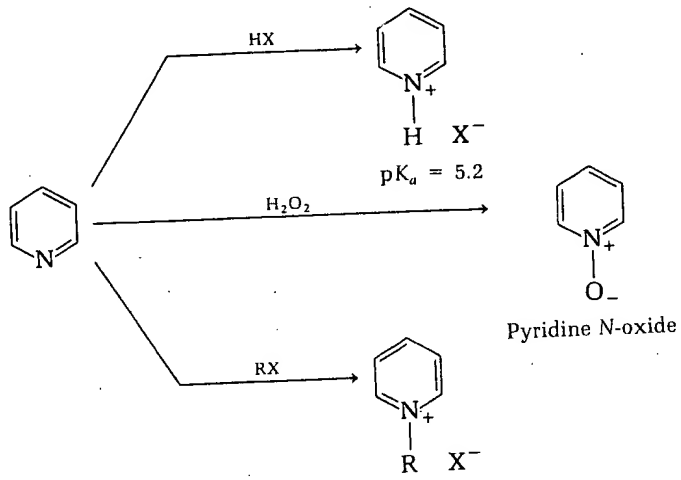


Isoquinoline

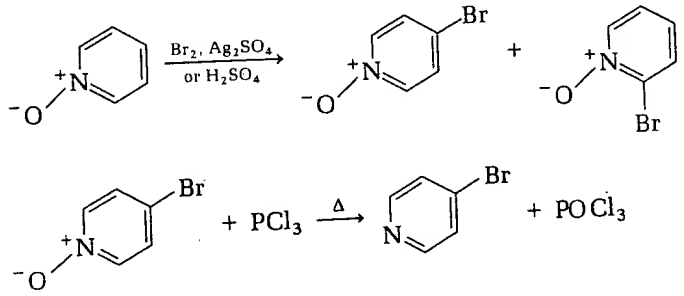


Acridine

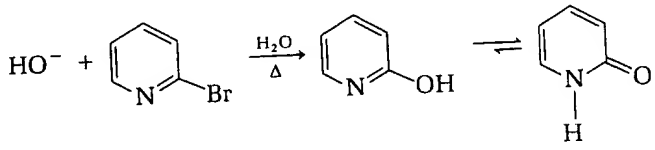
As an amine, pyridine reacts with acids to form pyridinium salts, comparable in acid strength to carboxylic acids. Pyridines react with peroxides to form *N*-oxides, and with unhindered alkyl halides to form *N*-alkyl pyridinium salts.



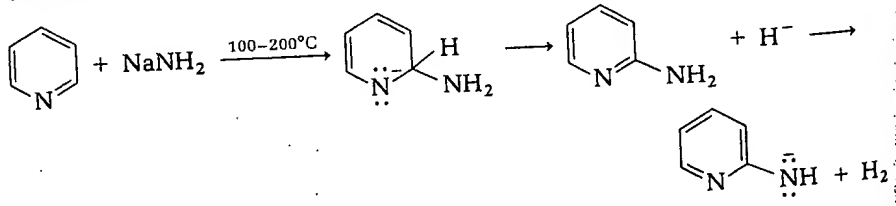
Toward electrophiles, pyridine behaves like a very deactivated benzene derivative, failing to undergo Friedel-Crafts acylation and undergoing sulfonation, nitration, or halogenation only under very vigorous conditions. Nitration or bromination can most effectively be conducted on the *N*-oxide, and 2- or 4-substituted pyridines are available by this means, after reduction of the *N*-oxide function:



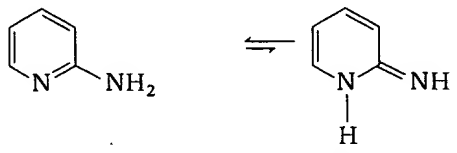
The 2- and 4-halopyridines show reactivity that is similar to that of 4-nitrohalobenzenes. They react with nucleophiles such as water or amines to give pyridones or aminopyridines. Reaction of pyridine with sodamide also gives 2-aminopyridine (Chichibabin reaction). These nucleophilic addition reactions occur easily in the 2 and 4 positions because of the conjugating electron-withdrawing effect of the imine function:



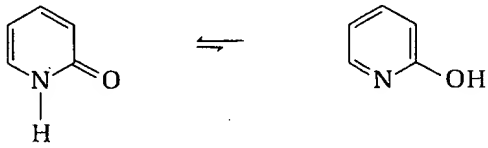
Chichibabin reaction:



The 2-aminopyridines exist primarily as the amine tautomer, as shown. The 2-hydroxypyridines prefer the pyridone tautomeric form in water, although the hydroxypyridine form may be more stable under other solvent conditions. The positions of these two tautomeric equilibria apply generally to heterocycles and provide a key feature of the molecular recognition responsible for the genetic code (Chapter 29):



2-Aminopyridine, more stable less stable



2-Pyridone, more stable 2-Hydroxypyridine, less stable

Problem 34·17 Predict the products of the following reaction sequences:

(*a*) 4-Bromopyridine + CH_3I ⟶ product + NH_2CH_3 ⟶ $C_7H_{10}N_2$

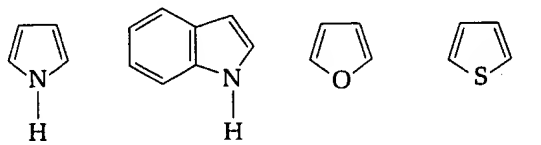
(*b*) 2-Methylpyridine + benzaldehyde $\xrightarrow{\text{base}}$ $C_{13}H_{11}N$

(*c*) Pyridine *N*-oxide + sodium cyanide ⟶ $C_6H_4N_2$

Problem 34·18 A 2- or 4-vinylpyridine has some of the properties of an acrylic ester. What properties do the two substances share? Explain.

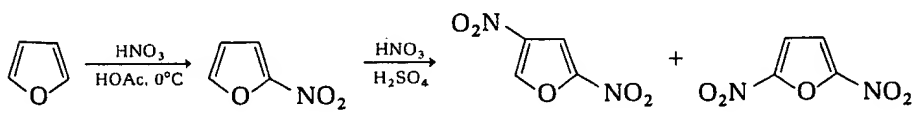
34·12 The Chemistry of Pyrrole, Indole, Furan, and Thiophene

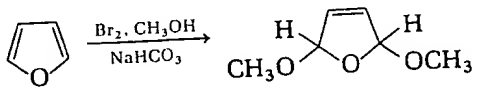
The five-membered heterocycles vary markedly in their degree of aromatic stabilization:



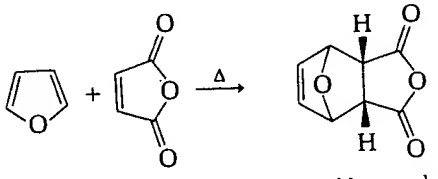
Pyrrole Indole Furan Thiophene

Thiophene is the most stabilized and behaves very much like an activated benzene derivative, undergoing electrophilic substitution more readily in the 2 than in the 3 position. Furan is the least stabilized and shows many properties expected of a diene or an enol ether. It and many of its derivatives are readily polymerized by strong acids:



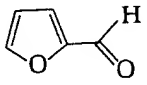


Addition, rather than substitution



Diels-Alder product

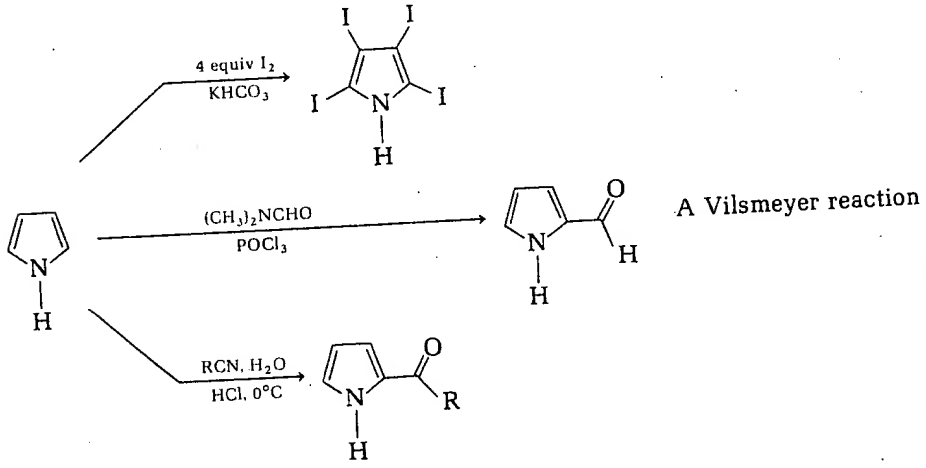
The most abundant furan derivative is furfural,



Furfural

obtained by acidic decomposition of corncobs.

Pyrrole shows aromaticity to the extent that it undergoes substitution, rather than addition, with electrophilic reagents. It behaves like a very strongly activated benzene derivative:



A Vilsmeyer reaction

Because of its high nucleophilicity, pyrrole is very susceptible to acid-catalyzed decomposition. It is stabilized by conjugation with electron-withdrawing substituents, such as formyl or carbethoxy.

Problem 34·19 What product do you expect if 2,5-diphenylfuran is subjected to acid-catalyzed hydrolysis? Condensation of this product with ammonia yields a substance $C_{16}H_{13}N$. What is its structure?

Problem 34·20 The substance 2,5-dihydroxyfuran is much less stable than a tautomer into which it is rapidly converted. What is the structure of the tautomer? What is its name?